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WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

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HUI, SAN MING R	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/072,010
Filing Date: October 25, 2001
Appellant(s): NYCE, JONATHAN W.

Albert Halluin
Wilson Sonsini Goodrich & Rosati
650 Page Mill Road
Palo Alto, CA 94304-1050
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 22, 2006 appealing from the Office action mailed March 2, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

An Appeal Brief is filed on co-pending application 10/410,955

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

4,956,355	Prendergast	9-1990
5,527,789	Nyce	6-1996

Lieberman et al. , Pharmaceutical Dosage Forms, page 110

Remington: The Science and Practice of Pharmacy", 17th Ed, by Alfonso R Gennaro, 1985, page 150

"Pharmaceutical Dosage Forms and Drug Delivery System" by Ansel et al. 6th Ed, page 454-455

Kelly and Hill, Chapter 24: Asthma in Pharmacotherapy - A Pathophysiologic Approach, 2nd ed., 1992, pages 408-449 by Elsevier

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 160-162 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prendergast (4,956,355 of record) in view of Lieberman et al. (Pharmaceutical Dosage Forms, page 110, of record) and "Remington: The Science and Practice of Pharmacy", 17th Ed, by Alfonso R Gennaro, 1985, page 1505.

Prendergast discloses that particular dehydroepiandrosterones (DHEA) herein are useful in a pharmaceutical composition or a pharmaceutical formulation of enteral, parental, injectable, topical, inhalations or nasal inhalation administration (see col.5 lines 32-64, 49 and 63-64). See abstract, col.1 lines 36-57, col. 4-5 and claim 6. Prendergast also discloses the effective amounts of dehydroepiandrosterones in the composition and other agents and pharmaceutically acceptable excipients within the instant claim in the compositions therein (col.5).

Prendergast does not expressly disclose the particular ranges of particle size herein, about 1.0-5 μm in size.

However, suitable particle sizes for inhalation are generally known and available to one of ordinary skill in the art. For example, "Remington: The Science and Practice of Pharmacy", 17th Ed, by Alfonso R Gennaro, 1985, teaches that the optimum particle size for preparation into the pulmonary cavity is of the order of ½ to 7 μm (see page 1505).

"Remington: The Science and Practice of Pharmacy", 20th Ed, by Alfonso R Gennaro, teaches that the optimum size for inhalations is known to be 0.5- 7 μm into the pulmonary cavity (see page 735 the right column).

The book "Pharmaceutical Dosage Forms and Drug Delivery System" by Ansel et al. 6th Ed, page 454-455, teaches that the fine particle size for inhalations is known to range 0.5-5 μm (see page 455, the left column).

Lieberman et al. teaches that a skilled artisan in pharmaceutical science would clearly knowledge that the granulation, determination of size, or size reduction of a solid

pharmaceutical formulation, e.g., in nasal inhalation formulation, have several benefits, for example, as taught in a text book "Pharmaceutical Dosage Forms" Tables, (Volume 2) Ed. by Herbert A. Lieberman, Leon Leachman, and Joseph B. Schwartz (1989) at page 110.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine and granulate the dehydroepiandrosterone sulfate particles in range of size herein for nasal inhalation.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine and granulate the dehydroepiandrosterone sulfate particles in range of size herein for nasal inhalation, since particular dehydroepiandrosterone sulfate (DHEA-S) herein are known to be in a pharmaceutical composition for inhalations or nasal inhalation administration based on Prendergast.

As discussed above, the optimum size for inhalations is known to be ½ to 7 μm into the pulmonary cavity according to "Remington: The Science and Practice of Pharmacy", and the fine particle size for inhalations is known to range 0.5-5 μm according to "Pharmaceutical Dosage Forms and Drug Delivery System". Thus, the dehydroepiandrosterone sulfate compositions of Prendergast for inhalations or nasal inhalation intrinsically comprise dehydroepiandrosterone sulphate particles having about 1-5 μm in size.

Moreover, the known teachings of these books clearly support the examiner's position that it is obvious to one of ordinary skill in the art that using conventional techniques to make inhalable, respirable or nasal formulation of the known active

agents are considered well within the skill of artisan in pharmaceutical science, involving merely routine skill in the art, in addition to suitable particle sizes for nasal inhalation generally known and being available to one of ordinary skill in the art.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claims 187-189 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prendergast, Lieberman et al. and Remington as applied to claims 160-162, 165 above, and further in view of Kelly and Hill, Chapter 24: Asthma in Pharmacotherapy – A Pathophysiologic Approach, 2nd ed., 1992, pages 408-449 by Elsevier.

Prendergast, Lieberman et al. and Remington teach the composition of DHEA-S in the particle size as about 1-5 μm.

The references do not expressly teach the particle size of DHEA-S as 15-500μm.

Kelly and Hill teaches the devices for delivering therapeutic aerosols generate particles with aerodynamic diameters from 0.5 to 35μm in diameter (See page 432, col. 2, least two paragraph).

It would have been obvious to one of ordinary skill in the art at the time of invention to formulate the particle size of the DHEA-S composition into 15-500μm.

One of ordinary skill in the art would have been motivated to formulate the particle size of the DHEA-S composition into 15-500μm. It is known that particle size of 0.5-35μm in diameter as useful in delivering drug particles into the lung. Therefore, formulating DHEA-S composition into particle size to 35μm, for example, would be reasonably expected to be useful.

Claims 160-162, 165 and 187-190 are rejected under 35 U.S.C. 103(a) as being unpatentable Nyce (5,527,789, of record) in view of Lieberman et al.,"Remington: The Science and Practice of Pharmacy", and Kelly and Hill.

Nyce discloses a pharmaceutical composition comprising the instant DHEA having the chemical formula (I) in a therapeutically effective amounts and the instant ubiquinone having the chemical formula (II) with n being from 1 to 12, 1 to 10, 6 to 10, or 10, in the therapeutically effective amounts, and a pharmaceutical carrier or diluent (see abstract, claims 13-19). Nyce also discloses the particular effective amounts of DHEA, i.e., 1-3600 mg/kg, 5-1800 mg/kg, or 20-100 mg/kg (see col.6 lines 6-7); and the particular effective amounts of ubiquinone, i.e., 1-1200 mg/kg, 30-600 mg/kg, or 50-150 mg/kg (see col.5 lines 64-66), within the instant claimed range, about 0.1-49% or about 1-20% w/w, since converting the known actual amount by actual weight to weight percentage in a composition, w/w, is considered well within conventional skills in pharmaceutical science, involving merely routine skill in the art. The pharmaceutical composition of Nyce further comprises a preservative, an antioxidant, a flavoring agent (e.g., sugar, see col.7 line 10), a buffering agent, a dispersant, or a surfactant (see col.6

line 67 to col.8 line 1, and col.7 lines 33-38) an inert base, glycerol (glycerin, see col.7 line 11-12). Nyce also discloses the instant forms of the formulation, e.g., nasal spay (see col.7 line 17) oral, rectal, topical, transdermal, nasal, or parenteral including injectable (see col.5 lines 37-41, col.6 lines 40-67), in a solution (an aqueous liquor), suspension.

The cited prior art does not expressly disclose the particular particles of the active agents having size herein, about 1-5 μm or about 15-500 μm in size.

However, suitable particle sizes for inhalation are generally known and available to one of ordinary skill in the art. For example, "Remington: The Science and Practice of Pharmacy", 17th Ed, by Alfonso R Gennaro, 1985, teaches that the optimum particle size for preparation into the pulmonary cavity is of the order of ½ to 7 μm (see page 1505).

"Remington: The Science and Practice of Pharmacy", 20th Ed, by Alfonso R Gennaro, teaches that the optimum size for inhalations is known to be 0.5-0.7 μm into the pulmonary cavity (see page 735 the right column).

The book "Pharmaceutical Dosage Forms and Drug Delivery System" by Ansel et al. 6th Ed, page 454-455, teaches that the fine particle size for inhalations is known to range 0.5-5 μm (see page 455, the left column).

Lieberman et al. teaches that a skilled artisan in pharmaceutical science would clearly knowledge that the granulation, determination of size, or size reduction of a solid pharmaceutical formulation, e.g., in nasal inhalation formulation, have several benefits, for example, as taught in a text book "Pharmaceutical Dosage Forms" Tables, (Volume

2) Ed. by Herbert A. Lieberman, Leon Leachman, and Joseph B. Schwartz (1989) at page 110.

Moreover, suitable particle sizes for inhalation are generally known and available to one of ordinary skill in the art. For example, "Remington: The Science and Practice of Pharmacy", 20th Ed, by Alfonso R Gennaro, teaches that the optimum size for inhalations is known to be 0.5-0.7 μm or ½ to 7 μm into the pulmonary cavity (see page 735 the right column). The book "Pharmaceutical Dosage Forms and Drug Delivery System" by Ansel et al. 6th Ed, page 454-455, teaches that the fine particle size for inhalations is known to range 0.5-5 μm (see page 455, the left column).

Furthermore, Kelly and Hill teaches the devices for delivering therapeutic aerosols generate particles with aerodynamic diameters from 0.5 to 35μm in diameter (See page 432, col. 2, least two paragraph).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine and granulate the dehydroepiandrosterone sulfate particles in range of size herein for nasal inhalation.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine and granulate the dehydroepiandrosterones particles in range of size herein for nasal inhalation, since the nasal formulation or composition comprising two instant active agents is known based on Nyce. According to conventional techniques to make inhalable, respirable or nasal formulation of the known active agents are considered well within the skill of artisan in pharmaceutical science,

involving merely routine skill in the art, in addition to suitable particle sizes for nasal inhalation generally known and being available to one of ordinary skill in the art.

The known teachings of these books clearly support the examiner's position that it is obvious to one of ordinary skill in the art that using conventional techniques to make inhalable, respirable or nasal formulation of the known active agents are considered well within the skill of artisan in pharmaceutical science, involving merely routine skill in the art, in addition to suitable particle sizes for nasal inhalation generally known and being available to one of ordinary skill in the art.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant is further requested to note that it is well settled that "intended use" of a composition or product, will not further limit claims drawn to a composition or product. See, e.g., *Ex parte Masham*, 2 USPQ2d 1647 (1987) and *In re Hack* 114, USPQ 161.

(10) Response to Argument

Appellant's rebuttal arguments in pages 4-6 in the Appeal Brief filed December 22, 2006 averring the failure of the cited prior arts to provide motivation to combine due to Prendergast's method of treating HIV infection as systemic treatment, are not convincing. Examiner notes that the claims are directed to a composition comprising DHEA-S. The issue at hand is not how the composition will be effected in the body.

Prendergast clearly teaches the routes of administration can be inhalation. The primary reference does not teach the herein recited particle size. However, the secondary references, i.e., Remington and Ansel, both well-known pharmaceutical text references, teach that the optimal particle size for inhalation as 0.5-7 μm or 0.5 -5μm. Thus, one of ordinary skill in the art would be motivated to formulate the dehydroepiandrosterone sulfate compositions of Prendergast for inhalations or nasal inhalation comprising dehydroepiandrosterone sulphate particles having about 1-5 μm in size.

Appellant's rebuttal arguments in pages 6-7 in the Appeal Brief filed December 22, 2006 averring Examiner using hindsight reasoning and the cited prior arts fails to teach to deliver DHEA-S in any other route of administration other than oral are unconvincing. The arguments are directed to the intended use of the composition. Since the claims are directed to the composition of DHEA-S, the arguments directed to the intended use of how to use the powder composition are considered moot. Furthermore, Prendergast clearly teaches the DHEA-S composition being delivered in various routes of administration including inhalation and oral. Therefore, the citing of Table 1 in Remington is misplaced. The purpose of citing Remington is merely to show the state of the art with regard to optimal particle size for inhalation. Therefore, possessing the teachings of the cited prior arts, one of ordinary skill in the art would have been motivated to optimize the particle size of DHEA-S according to the route of administration desired and in the instant case, the inhalation delivery, to the optimal particle size such as those herein claimed.

Appellant's rebuttal arguments in page 7 in the Appeal Brief filed December 22, 2006 averring the teaching away by Lieberman are not convincing. Especially "Lieberman presents a table that demonstrates how different molecular compositions give rise to very different properties in the same size powders" is disclosed in Lieberman, pages 36-37 and such citing is not of record. Appellant did not provide the Office the copy of these pages. Anyhow, page 110 in Lieberman clearly teaches about size reduction of pharmaceutical particles. Furthermore, it is also noted that other factors also contributing in formulating powder formulation, as noted by the Appellant in page 7 of the Brief. However, the teachings of Lieberman clearly reflects the state of the art then one of ordinary skill in the art would have envisioned these factors when optimize the particle sizes. There is no teaching away in Lieberman since one cannot apply piecemeal analysis to attack the reference individually. The citing of Lieberman is to show that particle size reduction is well-known to one of ordinary skill in the art. Therefore, taken with the teachings of the cited prior arts, one of ordinary skill in the art would have been motivated to optimize the particle size of DHEA-S for optimal delivery via inhalation.

Appellant's rebuttal arguments in pages 8-9 in the Appeal Brief filed December 22, 2006 averring the presence of unexpected results are not convincing. The alleged unexpected results are directed to the use of DHEA-S inhalation to treat asthma. DHEA-S is a steroidal compound with a steroidal structure. In the method of treating asthma, the inhaled glucocorticoids (also steroids) produce does-dependent suppression of the adrenal cortex, but much less than systemic glucocorticoids. It is

clear that the side effect of inhaled glucocorticoids is much less than systemic glucocorticoids. Moreover, the dose to produce the same anti-asthma potency is much less for inhalation therapy than in systemic therapy (See Kelly and Hill, page 431, col. 1, second and third paragraphs). From the general textbook teachings, which one of ordinary skill in the art is charged to have possession, it would be clear that the so-called unexpected results are not unexpected. In fact, it would be obvious to administer the steroid via inhalation rather than systemically because the inhalation dose is smaller than that of systemically and therefore, the side effect will be smaller. Accordingly, possessing the teachings of the cited prior arts, one of ordinary skill in the art would see that the unexpected results are not present. Even argenudo, the claims are directed to composition of DHEA-S with a certain particle size. They are not directed to the use of such composition. There is no comparison as to the different particle sizes of DHEA-S in the study and it appears that no criticality of the herein claimed particle size is demonstrated.

Appellant's rebuttal arguments in pages 9-11 in the Appeal Brief filed December 22, 2006 averring the cited prior arts' failure to support routine optimization are not convincing. Examiner notes that in four of the cited references, Remington, Ansel, Kelly and Hill, and Lieberman, they all disclose the pharmaceutical particle sizes and size reduction, and/or optimal particle size for inhalation. These references are textbook references that are well-known in the art, and one of ordinary skill in the arts are charged to have possession. And yet, Appellant still thinks that it is not routine to optimize the particle size when all four references teach the similar theme of optimal

particle size for inhalation, and/or particle reduction. Examiner notes that Appellant has not cited any reference to teach the contrary. Appellant also fails to show the criticality of the specific particle size herein claimed. Accordingly, the claims are properly rejected under 35 USC 103(a).

Appellant's rebuttal arguments in pages 12-14 in the Appeal Brief filed December 22, 2006 averring the failure of the cited prior arts to teach or suggest the herein claimed particle size are not convincing. It is not clear why the teaching of one range (namely 1-5μm) would be teaching away from the other (15-500μm). Prendergast clearly teaches the routes of DHEA-S delivery can be enteral, parental, injectable, topical, inhalations or nasal inhalation administration (see col.5 lines 32-64, 49 and 63-64). As such, different particle sizes would be suitable for different routes of administration. Furthermore, even *argenudo*, Kelly and Hill clearly teaches the particle size overlaps with what is recited. Therefore, possessing the teachings of the cited prior arts, one of ordinary skill in the art would have been motivated to optimize the particle size for optimal delivery of DHEA-S, absent evidence to the contrary. No such evidence is seen to be present herein.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

San-Ming Hui
Primary Examiner
Art Unit 1617

Conferees:

SHENGJUN WANG
PRIMARY EXAMINER

Shengjun Wang, Ph.D.
Primary Examiner
Art Unit 1617

Sreeni Padmanabhan, Ph.D.
SPE
Art Unit 1617

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER